Patient-reported outcomes in metastatic castration-resistant prostate cancer

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Abstract

Many novel therapies are available for use in metastatic castrate resistant prostate cancer (mCRPC), some of which convey significant progression-free and overall survival benefits. Delaying progression and palliation of symptoms are primary therapeutic aims, so it is vital to ensure that benefit/harm ratios are acceptable through systematic measurement of patient reported outcomes (PROs) using validated tools. We appraised mCRPC clinical trial publications over the past 5 years and found that PROs were either not being measured routinely or often failed to be reported adequately hampering evaluation. Improvements are needed as data collected directly from patients, not just physician collected safety data and adverse events, are crucial to inform decision-making about treatment options.

Introduction

The most common non-cutaneous cancer affecting men is prostate cancer; it is the second commonest cause of cancer-related death in the US and the third in Europe[1]. Approximately 25-30% of men who initially present with localised or locally advanced disease will have a recurrence and many will require systemic treatment with androgen deprivation therapy (ADT). ADT can control the disease for some years but the prostate cancer ultimately progresses and requires the addition of different therapeutic approaches. Unfortunately the majority, who present with advanced or metastatic prostate cancer, will progress to this stage of castrate resistant prostate cancer (CRPC) despite an initial response to ADT.[2]

The most common first line chemotherapy treatment for metastatic CRPC (mCRPC) is docetaxel plus prednisone.[3] Additional more novel agents have expanded the treatment options including radium-223 dichloride [Ra223], and Sipuleucel-T (an autologous cellular immunotherapy).[4,5] Advancing prostate cancer is not uniformly refractory to further hormonal manipulation and androgens, and disease progression is frequently dependent on androgen synthesis and androgen receptor interactions. CRPC which is still hormone sensitive, has been clearly characterised by its response to new drugs such as abiraterone acetate (androgen biosynthesis inhibitor) and enzalutamide (androgen receptor inhibitor). These compounds have demonstrated survival benefits for patients in Phase III clinical trials in the docetaxel naïve setting and also in men who have progressed after chemotherapy.[6-9] Second line chemotherapy with cabazitaxel has also demonstrated benefits in overall survival when compared with mitoxantrone.[2]

Many have raised concerns about the infinite demands being made on finite healthcare budgets. Cancer drugs in particular have come under intense scrutiny as they are invariably expensive and their actual benefits to patients, let alone society, are often incompletely measured and poorly elucidated. Increasing numbers of men globally have mCRPC and want access to novel therapies, which although approved may not be available having failed health technology assessments. Traditional clinical outcomes such as Progression Free Survival (PFS) and Overall Survival (OS) are well measured in trials but patient perspectives less so. Frequently the quality of the evidence and knowledge available about issues other than survival that might influence decision makers is inadequate. There is still far too great reliance placed on clinician adverse event (AE) recording within trials rather than directly from patients and thus many side-effects go under-reported, under-recognised and under-treated. Not only is the reliability of AE reporting between clinicians poor[10] but patients record many symptoms more frequently and at a greater severity than ratings made by clinicians using CTCAE (Common Terminology Criteria for Adverse Events) criteria.[11] Certain side effects may have far more relevance to the decision making process of men than is realised, for example what may be termed relatively minor symptoms by a clinician may in fact have a profound effect on certain individuals and strongly influence their treatment choices.[12]

Men with mCRPC report significantly poorer quality of life (QoL) than other groups of men with prostate cancer with priority areas being fatigue, pain, and decreased physical activity.[13] From the patient's perspective, optimal treatment for advanced prostate cancer may be a function of the patient's willingness to make trade-offs between attributes such as efficacy and tolerability. Treatment choices involve complex decision-making that

might not always appear rational to a clinical scientist. Even when the information provided is optimal, individual patients may have preferences influenced by expectations about their likely ability to continue to pursue hobbies, employment, and other activities. Again hard data regarding these salient issues from a patient's perspective are often missing. The experience and acceptability of treatment may be linked to the expectations about therapeutic intent, likely side-effects and trade-offs between these and control of the cancer, which in turn may be determined by the information provided by Health Care Professionals (HCPs). The knowledge and perceptions HCPs themselves may have about the impact of treatments on more patient related concerns is uncertain, especially if QoL type data are generally unavailable.[14] To this end, The American Society of Cancer Oncology (ASCO) and its European counterpart (ESMO) have published papers this year suggesting that new scales are needed to determine the magnitude of clinical benefit from a patient's perspective. [15,16]

Patient reported outcome measures (PROMs)

Both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have recognised that good quality data from PROMs are important when evaluating drugs in patients for whom palliation of symptoms is an important therapeutic goal; consequently they have published guidance and recommendations for use of PROMs in clinical trials.[17] [18] Despite this, evidence from ClinicalTrials.gov (2007–2013) identified only 29% (3947/13,584) of all oncology trials as using one or more PROM and merely 2453/13, 584 (18%) of oncology trials listed a PRO as a primary or secondary outcome.[19] Although these figures showed an increase since the FDA PRO guidelines publication, the omission of PROs is a sorry reflection on the value placed on such measures.

We wished to critique publications over the past 5 years, of mCRPC treatment trials where the therapeutic aims are control of progression and amelioration of symptoms of disease. We wanted to see if studies had included good quality PRO data. Our approach was not a systematic review, but we did use criteria similar to those specified by Clavert and colleagues when making some evaluation of the quality. [20] We considered 5 areas:- (1) identification of PROs as a primary or secondary outcome (2) hypothesis and relevant domains described (3) evidence provided or cited of the validity and reliability of the PRO (4) explicit statements about statistical approaches for dealing with missing data and (5) some discussion about PRO–specific limitations of study findings/generalisability of results to other populations and clinical practice. For us to consider the reports to be examples of good quality, they had to cover at least 4 of these quality areas and demonstrate convincingly that the investigational drug had improved QoL or pain outcomes as well as efficacy. We deemed publications as adequate if only 3 areas were covered, and poor if any improvements were not compelling and/or 2 or fewer key areas were mentioned.

Effects of mCRPC treatments on QoL and pain palliation

The types of patient reported outcome measures that were used in the recent mCRPC treatment trials we accessed are shown in Table 1.

Table 2 lists the reported effects of mCRPC treatments on QoL and pain palliation by drug.

Enzalutamide

Trials that have been well conducted as far as PROs are concerned include two assessing enzalutamide. Fizazi and colleagues[21] reported the clinical endpoints and overall QoL for the AFFIRM trial but more detailed QoL analyses were provided in a separate publication by Cella and colleagues[22] and showed that enzalutamide significantly improved QoL. Following 25 weeks of treatment the mean FACT-P total score decreased by 1.52 points with enzalutamide compared with 13.73 points with placebo ($p<0.001$), reflecting a larger deterioration in the QoL of those men receiving placebo. In addition there were significant treatment differences favouring enzalutamide for all FACT-P subscales and indices, including pain, whether analysed by mixed effects model for repeated measures that assumes missing data are at random, or a pattern mixed model that assumes missing data are not at random.

In the PREVAIL trial QoL and pain were measured at baseline with the FACT-P, EQ5-D and the BPI-SF and thereafter at regular periods throughout study treatment.[23] Improvement in QoL was defined as an increase, and deterioration as a decrease, in the score at any post baseline assessment by pre -determined thresholds. These thresholds were based on score range changes that are clinically meaningful to patients. The authors detailed succinctly the components of the questionnaires in a table for ease of reference. The results showed that enzalutamide was associated with reduced risk of, and delayed time to QoL deterioration, pain progression and occurrence of SREs.

Abiraterone

There are a comprehensive series of publications reporting PROs in the Phase III COU-AA-301 RCT a double blind placebo controlled trial of abiraterone + prednisone versus placebo + prednisone. The pain, QoL and fatigue analyses were all published separately.[24-26] Pain was assessed using the BPI-SF at baseline, day 15 of cycle 1 and day 1 of each treatment cycle thereafter until discontinuation. Analgesia use was measured and time to occurrence of each skeletal-related event (SRE). Completion rates of the questionnaires were reasonably good and the authors used prospectively defined response criteria. Pain palliation was assessed in those who had clinically significant baseline pain, whereas all other analyses were done on an overall intention to treat analysis. The trial results showed that abiraterone + prednisone produced significant pain palliation and faster pain palliation in patients with clinically significant pain at baseline as well as delaying time to first SRE [24]. Harland and colleagues reported the QoL data from the same trial using the FACT-P [25]. The analysis was performed only in those patients with clinically significant functional impairment at baseline on the basis that they could not evidence any improvement in QoL. Arguably a clearer picture of how the drugs affect QoL may have been achieved if a responder analysis showing the proportion of patients who improved, deteriorated or stayed the same over time had been done. Significant improvements on the FACT-P total score in favour of abiraterone were noted ($p<0.0001$), including all subscale scores, apart from social/family well-being. Sternberg and colleagues[26] described the fatigue results from the same study using the Brief Fatigue Inventory. The questionnaire was completed at baseline (approximately 14

days before the first dose of study treatment) and on the first day of each treatment cycle until treatment was discontinued. Clinically meaningful changes were pre-specified before conducting the analyses and similar to Harland[25], analyses were confined to those with significant clinical fatigue at baseline (i.e. scores of $\geq$ 5). The report demonstrated that abiraterone acetate and prednisone provide substantial and meaningful improvements in self-report fatigue in patients with mCRPC after docetaxel chemotherapy.[26]

Basch and colleagues used the FACT-P and BPI-SF to examine QoL and pain palliation respectively in the Phase III trial COU-AA-302 (abiraterone acetate plus prednisone versus prednisone alone in chemotherapy-naive men with mCRPC) [27.] The pain analyses were detailed, and showed that abiraterone and prednisone delayed time to progression of mean pain intensity and pain interference as well as time to QoL deterioration.

In summary all these publications together showed an advantage of aberiterone and prednisone to patients in terms of efficacy, pain control and QoL.

Docetaxel

The Phase II trial of docetaxel +/- estramustine reported results from the EORTC QLQ C30, BPI and analgesia use. [28] Data from 59/79 patients were included in the analysis. The authors reported the proportions of patients who improved, remained stable or worsened from baseline, and there were no significant changes in the EORTC-QLQ C30 scales or pain scores during treatment. Probably the most interestingly feature of this study was the finding that the baseline QoL measurements appeared to predict treatment responders from non-responders.

A publication of an RCT in which men received either continuous (n=75) or monthly intermittent (n=73) docetaxel treatment failed to show any significant differences in QoL (EORTC QLQ C-30) or pain (BPI-SF). However this may have been due to the timing of the assessments. Despite QoL being cited as the primary outcome of the study the publication lacks important details about missing data and how the analyses were conducted. [29]

Cabazitaxel

The TROPIC trial was a prospective Phase III RCT that involved 755 mCRPC patients who had progressed during or after docetaxel based chemotherapy. [2] Follow-up pain and QoL data were measured retrospectively with the McGill-Melzack pain questionnaire in a sub group of patients who had survived for 2 years.[30] The ECOG score was employed as a QoL measure; however this is not a PRO, rather a performance score which is assessed and completed by the clinician. The sample size was small, there was poor reporting of pain data and unsurprisingly no significant differences were found between groups.

In a follow on Phase III/IV trial to facilitate access to cabazitaxel and evaluate more formally QoL, 112 men with mCRPC completed the EQ5D with the general 'health today' VAS at baseline, following alternate cycles and at the end of treatment.[31] The choice of this instrument (used predominantly to provide a utility score for use in health economic models) limited the ability to collect comprehensive information about any toxicities from

a patient's perspective and few formal analyses were carried out despite the claim of a trend to significant improvement in QoL.

Radium-233 chloride

Pain palliation was the primary endpoint in the Phase II trial of radium-233 chloride, in which patients were randomised to a single intravenous dose of 5, 25, 50 or 100kBq/kg radium-233.[32] The effect of the treatment was documented by patients' self-assessment of pain using a VAS, the BPI and analgesia use. As is the case with many studies of patients with metastatic disease, few patients from the original sample survive for follow up; at 12 months data were available on 32/100 and 8/100 at 24 months. The primary endpoint pain index (VAS and analgesia use) was used to classify patients as pain responders or non-responders. Results showed that up to 71% of patients had a pain response at week 8 after a single radium injection. Small numbers and incomplete follow up limit generalisability of results.

^{177}Lu-EDTMP

Agarwal and colleagues examined in a Phase II RCT trial high v low dose ^{177}Lu-EDTMP for bone pain relief in patients with bone metastases (N=32 mCRPC; N=12 breast).[33] They used the McCaffery VAS to measure pain, and the Karnofsky Performance Score (KPS) for QoL. Pain relief was assessed in terms of changes in average baseline pain v average scores at 1,2,4,5,7,12 and 16 weeks. They reported a progressive decrease in pain on the VAS from baseline up to 4 weeks, and claimed an improvement in QoL. However the KPS is not a PRO measure but a clinician completed performance scale originally designed to determine nursing workload and staffing requirements.

Denosumab

The final paper reports results from a pooled analysis from three identically designed double blind Phase III studies comparing subcutaneous denosumab with intravenous zolendronic acid in 5,544 patients with bone metastases, 1,901 of whom were men with mCRPC.[34] Analysis of the data showed that denosumab significantly delayed time to an increase in pain severity in those with pain at baseline and delayed pain for those with no /mild pain at baseline. Although the statistics are very thorough, the pooled analyses make it hard to determine benefits for the prostate patients alone.

Conclusions/perspectives

The increasing numbers of therapeutic endeavours to improve the outlook for men with mCRPC is welcome. Unfortunately there are still insufficient patient outcome data from trials. Importantly even less is known about the impact of novel therapies when used in other clinical settings where patients may have co-morbidities and characteristics that make them ineligible for treatment within a trial. Routine collection of a standard set of outcomes such as those recommended for prostate cancer trials[35] or more recently others developed by the ICHOM group [36], which come directly from patients in clinic, might be invaluable to build up sufficient 'real-world' data to aid decision-making.

Discussion

Both disease burden and mCRPC treatments can have a deleterious impact upon QoL. Pain is the most frequently observed symptom in men with mCRPC and appropriate analgesia is often underutilised.[13,37] In comparison to other men with prostate cancer, those with mCRPC report significantly poorer QoL, due to pain, fatigue, and decreased physical activity.[38] These areas of concern need to be captured fully when palliation is a therapeutic aim. PROs have been included in more recent treatment trials but usually as secondary endpoints with the exception of the Phase II studies. [29, 32, 33] Several articles contained opaque, post-hoc exploratory analyses with little or no clear evidence that the patient reported endpoints chosen had been established a priori. Much of the published work was characterised by inappropriate choice of instruments, poor statistical analyses or scanty reporting and inadequate interpretation of results. The statistical analyses in papers scrutinised included comparisons of mean scores at one time-point and no references to changes from baseline, to responder analyses and cumulative distribution function plots. Not all reports determined or utilised the published minimally important differences (MIDs) or clinically meaningful differences when comparing any changes in scores. Details about the handling of missing data, any imputation used, and sensitivity analysis to test if data were truly missing at random and ignorable were seen in remarkably few studies.

The variable quality of the analyses and reporting was often dependent as to whether or not PROs had been written up separately from the main efficacy papers in comprehensive publications such as those from the COU-AA-301 studies. [24-26] This is of course a dilemma when many researchers and journals give priority to papers containing more traditional safety data and adverse event reporting leaving little space for secondary endpoints such as PROs.

The continued dearth of quality PRO data from patients for whom palliation of symptoms is essential is both disappointing and surprising. The European Medicines Agency (EMA) provides broad recommendations on HRQoL (Health Related Quality of Life) in the context of clinical trials. [18] and the US Food and Drug Administration (FDA) has formal guidance setting standards for use of PROMs in support of product labelling claims.[17] An interesting paper published recently explored the reasons for rejection of PRO label claims among new molecular and biological license applications. It revealed that the FDA specifically questioned the content validity and/or validity of instruments in general, and there were often issues with the study design, data quality, or interpretation of results.[38]

Many novel products in the past decade have been shown to extend the lives of men with mCRPC but if they and their physicians are to make wise decisions about management options to the harms and putative benefits derived from different treatments must be addressed more adequately. Researchers need to employ well-validated, appropriate PRO measures in trials and to analyse and report the results more fully.

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Table 1: Patient Reported Outcome Measures used in recent mCRPC publications

Measure	Description
[40]EQ5D	Generic health outcome instrument that provides a simple descriptive profile and a single index value or utility score for health status. It comprises 5 dimensions: mobility, self-care, usual activities, pain /discomfort and anxiety /depression. Each dimension has a 3 category response scale: no problems, some problems, extreme problems.
[41]EORTC C30	30 item, generic cancer questionnaire that consists of five function scales (physical, role, emotional, cognitive and social, a global health scale, three multi item symptom scales (fatigue, nausea/vomiting and pain) and six single item scales (dyspnoea, sleep, appetite, constipation, diarrhoea, and financial difficulties due to disease). Response categories have 4 levels from 'not at all' to 'very much' apart from 2 items for overall physical condition and quality of life which use a 7 point scale. All scores from the scales and single item measures range from 0 to 100. A high scale score for global health status represents better quality of life
[42]PR25	Supplemental module to use in combination with the EORTC C30 for prostate specific issues (PR25) consisting of 25 items assessing urinary and bowel symptoms, sexual activity and functioning and side effects of therapy.
[43]FACT P	Comprises a generic core questionnaire (FACT-G) that comprises 27 items divided into 4 domains; physical, functional, emotional and social well-being. There is an additional subscale (FACT-P) with 12 prostate related specific concerns. All items are rated on a Likert scale from 0 to 4. The questionnaire produces an overall QoL score (FACT total) and subscale scores. Higher sum scores indicate a better quality of life. Summation of the physical, functional and prostate subscale scores produces a Treatment Outcome Index (FACT-TOI), which is considered the most sensitive indicator of patient related health in treatment RCTs.
[44]BPI-SF	The BPI-SF (9 items) recommended for use in clinical trials. It assesses pain intensity and the interference of pain with daily life. There is no scoring algorithm, but "worst pain" or the arithmetic mean of the 4 severity items is used to assess pain severity. Pain intensity is recorded as the worst pain in the past 24 hours. Pain interference is the mean score of all 7 items assessing the impact of pain on emotional well-being and physical activity providing an overall interference score.
[45]McGill-Melzack	Used by patients to monitor their pain over time and to determine the effectiveness of any intervention. It comprises 78 words, from which respondents choose those that best describe their pain experience. Scores are tabulated by summing values associated with each word; scores range from 0 (no pain) to 78 (severe pain).
[46]McCaffery VAS	This is a unidimensional visual analogue scale rating for pain, with 0 representing no pain and 10, pain that is intolerable
[47]BFI	The Brief Fatigue Inventory (BFI) assesses the severity and impact of cancer-related fatigue and its impact on daily functioning in the past 24 hours. Patients complete visual analogues scales from 0-10 rating their fatigue right now, usual fatigue, and worst in past 24 hours, followed by the interference of fatigue on general activity, mood, walking, work, relationships, and enjoyment of life. A global fatigue score is obtained by averaging all the items on the BFI.

Table 2: The effects of mCRPC treatments on QoL and pain palliation by drug

Author Year	Design and population	Measures & time points	Main Findings	Comments
ENZALUTAMIDE				
[21]Fizazi et al. 2014	AFFIRM Phase III RCT enzalutamide (E) v placebo (PL) following chemotherapy N=674 E N= 264 PL	**BPI-SF** Change from baseline to week 13 **FACT-P** Overall QoL, on individual domains & time to deterioration	Pain progression at week 13 for 174/625 (28%) E v 101/259 (39%) PL p=0. 0018. Mean treatment effects for pain severity and interference were sig better with E than PL. 22/49 (45%) E reported pain palliation at week 13 v 1/15 (7%) PL p=0. 0079. Overall improvement in HRQoL in E 275/625 [42%] than Pl (36/248 [15%]; p<0. 0001). Patients in the E had longer median time to HRQoL deterioration than PL p<0. 0001.	Excellent example of reporting QoL data with detailed analyses
[22]Cella et al. 2015	AFFIRM Phase III RCT As above	**FACT-P** completed before randomisation & at weeks 13, 17, 21, 25 & every 12 weeks while on study	After 25 weeks, the mean FACT-P total score decreased by 1.52 points with E compared with PL 13.73 points (P < 0.001). Significant treatment differences at week 25 favouring E were evident for all FACT-P subscales and indices.	Excellent example of reporting QoL data, reference to missing data. Used cumulative distribution function plots (CDF) in analysis.
[23]Loriot et al. 2015	PREVAIL Phase III RCT double-blind, placebo-controlled trial of enzalutamide (E) N=872 E N=845 PL	**FACT-P** baseline & during treatment **EQ5D + VAS** baseline & during treatment **BPI-SF** – baseline, weeks 13 & 25	Median time to deterioration in FACT-P total score 11.3mths (E) v 5.6mths (PL) (p<0.0001). Clinically meaningful improvements in FACT-P for E. EQ-5D & VAS showed sig. increase in proportion of patients	Excellent reporting of how PRO data handled and analysed

			in E than PL in time to worst pain longer in E than PL (p<0.0001).	
ABIRATERONE				
[24]Logothetis et al. 2012	Phase III RCT (COU-AA-301) double-blind, placebo-controlled trial of abiraterone + prednisone (AP) v placebo + prednisone (PP) post-docetaxel treatment N=797 AP N=398 PP	**BPI-SF** at screening (baseline), day 15 of cycle 1, and day 1 of every subsequent treatment cycle until the end of study treatment	Patients with clinically significant pain at baseline, AP resulted in sig palliation (157/ 349 [45%] *vs* 47/163 [28·8%]; p=0·0005) and faster palliation (median time to palliation 5·6 months *vs* 13·7 months p=0·0018) of pain intensity than PP.	Good exploratory analysis of pain data with skeletal related events. Prospectively defined response criteria that also included analgesic use.
[25]Harland et al. 2013	QoL aspect of Phase III RCT (COU-AA-301) As above	**FACT-P** at baseline and on day 1 of cycles 1, 4, 7, 10 & every six cycles until end of study treatment	Significant improvements FACT-P total score in 48% AP v 32% PP patients (p < 0.0001). Median time to deterioration in FACT-P total score was longer (p < 0.0001) for AP. Similar differences were observed in all FACT-P subscales, with the exception of the social/family well-being domain. Median time to improvement in the physical well-being domain and the trial outcome index was significantly shorter (p < 0.01) with AP.	Only patients with impaired HRQoL considered for the improvement analyses. Could have shown numbers who improved, declined or stayed the same over time. Highlights need for more frequent assessments.
[26]Sternberg et al. 2013	Phase III RCT (COU-AA-301) As above	**Brief Fatigue Inventory** at baseline (~14 days before the first dose of study treatment) & first day of each treatment cycle until treatment discontinuation	Compared with PP patients with clinically significant fatigue at baseline, AP significantly increased proportion reporting improvement in fatigue intensity (58% v 40%, P = 0.0001), improved fatigue interference (55% v 38%, P = 0.0075), &	Good paper but again analyses confined to those with fatigue at baseline.

			accelerated improvement in fatigue intensity (P = 0.0155).	
[27]Basch et al. 2013	Phase III (COU-AA-302) double blind placebo controlled trial of abiraterone + prednisone (AP) v placebo + prednisone (PP) in chemo naïve patients N= 546 (AP) N=542 (PP)	**BPI-SF** at screening, day 1 of each treatment cycle & at treatment end. **FACT-P** first day of cycles 1, 3, 5, 7 & then first day of every 3rd cycle & at treatment discontinuation.	Median times to progression of worst pain intensity were similar between groups. Median time to mean pain intensity also was longer with AP (p=0.049) and median time to interference with daily activities (p=0.005). AP significantly delayed time to QoL deterioration compared with PP, as assessed by FACT-P total score, general function and trial outcome index composite scores, prostate-cancer-specific scores, and all subscale scores except for social and family wellbeing (p<0.001).	Good reporting of data from BPI but only reported overall QoL scores.
DOCETAXEL				
[28]Caffo et al. 2011	Phase II RCT docetaxel (DOC) +/- estramustine N=95 mCRPC	**EORTC QLQ C30** **BPI** & analgesia use at baseline & after every two DOC courses The patients completing at least 2 questionnaires (at baseline and before the 3rd course) were considered evaluable	59/79 included in stats. Asymptomatic patients and responders had better baseline QoL than symptomatic patients and non-responders. No significant changes in QLQ-C30 scales during treatment except patients receiving DOC and estramustine, who experienced a significant decrease in pain. However big drop in completion of questionnaires across time.	Important study as it can identify responders from baseline assessment. Also reported proportions of patients who improved, remained stable and worsened from baseline.
[29]Caffo et al. 2015	RCT of continuous v 3 monthly intermittent DOC N=75 continuous N=73 intermittent	**EORTC QLQ C30** at baseline then every 2 courses **BPI-SF** used a difference of 2 points to assess either improvement or deterioration in pain	Failed to show any significant differences in QoL or pain between the groups possibly due to timing of assessments.	Not very detailed reporting of QoL data, no details of number of completed questionnaires across time

CABAZITAXEL				
[30]Bahl et al. 2013	Follow up on subgroup of patients who survived >2 years in TROPIC (cabazitaxel v mitoxantrone) to examine pain palliation. N=60 cabazitaxel N=31 mitoxantrone	**McGill-Melzack** pain questionnaire. Pain response & progression pre-specified end points. Pain assessed before each treatment cycle then every 6 weeks during the first 6 months of follow up & every 3 months thereafter until progression or initiation of other anticancer therapy.	No significant differences in pain progression or pain response between treatment groups, possibly due to small numbers. ECOG used as a measure of QoL –it is a performance score completed by the physician, not by the patient.	Poor reporting of data, small numbers, retrospective analysis, no reporting of missing data or data on number of questionnaires completed over time.
[31]Bahl et al. 2015	Phase III/IV trial to facilitate access to cabazitaxel and formal QoL evaluation N =112 mCRPC	**EQ5D-3L with VAS** at baseline, alternate cycles & end of treatment. Mean scores and paired analyses for EQ5D and also reported pain statement changes.	No formal statistical analyses conducted but report a trend to improved QoL at week 10 from baseline. Large error bars.	Poor reporting of QoL data, poor choice of instrument. The EQ5D is more used for economic analysis of treatments.
RADIOISOTOPES				
[32]Nilson et al. 2012	Phase II study of radium -223 chloride for palliation N=100 mCRPC	**BPI** VAS for pain index 1 week diary of daily baseline pain on VAS and patients' record of analgesic use and BPI Change from baseline at weeks 2, 4, 8, 12,16	Patients categorised as responders or non-responders. Dose dependent treatment effect. 71% pain response two weeks after administration.	Good example of use of BPI to measure pain but no other PRO data.
[33]Agarwal et al. 2015	Phase II RCT trial of high v low dose ^{177}Lu-EDTMP for bone pain relief in patients with bone metastases N=32 mCRPC N=12 breast	Daily diary **McCaffery** visual analogue pain scale, Pain relief assessed in terms of changes in average baseline pain v average scores at 1,2,4,5,7,12 and 16 weeks **Karnofsky performance score** (KPS) to measure QoL	^{177}Lu-EDTMP safe and effective alternative for bone pain palliation in patients with metastatic disease. Progressive decrease in pain on the VAS from baseline up to 4 weeks. Also improvement in QoL on the KPS but it is not a PRO.	Poor choice of instrument to measure QoL (the KPS), also a very small sample and little information about data handling.

DENOSUMAB				
[34]Von-Moos et al. 2013	Pooled data analysed from 3 identically designed double-blind phase III trials comparing sc denosumab 120 mg with IV zoledronic acid 4 mg monthly in patients with bone metastases from cancer N =2,046 breast N =1,901 mCRPC N=1,597 solid tumours.	**BPI-SF** for pain severity analyses. A score of ≤4 was considered no or mild pain and scores of >4 considered moderate to severe pain. 7 items from the BPI-SF measured pain interference with general activity, walking, work, mood, enjoyment of life, relations with others and sleep. **FACT-G** also completed at each monthly visit	Denosumab significantly delayed time to increase in pain by 0.3 months in those with pain at baseline and delayed pain by 1.8 months in those with no/mild pain at baseline. HRQL – FACT G MIDs. Fewer denosumab treated patients experienced clinically meaningful worsening from baseline.	Good analyses but pooling of data across cancer sites makes it difficult to determine exactly the benefits for mCRPC patients